

EDITORIAL COMMENT

The New Cholesterol Guidelines

Finally More Light Than Heat*



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I cannot remember practice guidelines more delayed, groundbreaking, and controversial than the 2013 American College of Cardiology/American Heart Association cholesterol guidelines (1). They are groundbreaking for using a new race-specific estimator to generate both 10-year and lifetime cardiovascular risk, for considering both stroke and coronary heart disease risk, and especially for replacing low-density lipoprotein (LDL) cholesterol goals with specific drug and dose treatment targets. Changes to our practice guidelines were badly needed, because the concept of “getting to goals” was never evidence based and because three-quarters of younger patients with myocardial infarctions would not have qualified for cholesterol treatment under the old guidelines just before their first events (2). The new guidelines have ignited a firestorm of dissent, ranging from perceived author conflict of interest to overestimation of risk to therapeutic nihilism regarding the benefits of statin treatment (3,4). Most of this criticism badly misses the mark, but how many and which patients should be considered for statin therapy are valid points for discussion.

First, what percent of a middle-aged population should be on statin therapy? This number is not difficult to estimate. I would recommend lifestyle modifications and statins to patients who already have had or I definitively know will experience atherosclerotic cardiovascular events in the future.

Assuming attainment of age 40 years, symptomatic coronary heart disease occurs in 49% of men and 32% of women over their lifetimes (5). Additionally, stroke, most of which is atherothrombotic, occurs in 16% of men and 21% of women age 55 to 75 years (6). Accounting for stroke plus heart disease overlap, ideally 61% of men and 48% of women age 40 to 75 years should be considered for statin therapy. Because we cannot definitively identify those who will have future events, treating an even larger percent of the population may be reasonable. Starting statins earlier than age 40 also may be reasonable, because Mendelian analysis suggests that earlier LDL cholesterol lowering is more beneficial (7). Taken from this point of view, the new guidelines’ estimated increase in recommended statin use from 38% to 49% of the middle-aged American population (8) should be recognized as strong support for the update rather than as criticism.

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The second valid point for discussion is whether the new guidelines correctly identify the specific patients who will benefit from statin therapy, namely, those who will experience future cardiovascular events. In this issue of the *Journal*, Johnson and Dowe (9) compare recommended statin use according to the 2001 and 2013 guidelines for patients with and without demonstrated coronary artery disease. In this single-center, retrospective study, they assessed coronary atherosclerosis burden by computed tomographic angiography in 3,076 subjects referred for angiography, using 3 scoring techniques. Unavailable pre-statin treatment values for total and low-density lipoprotein cholesterol were estimated from on-treatment data using assumed statin efficacy. Under the 2001 guidelines, 59% of patients with $\geq 50\%$ stenosis of the left main coronary artery and 40% of patients with $\geq 50\%$ stenosis of other branches would

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not have been treated. The comparable results for the 2013 guidelines were 19% and 10%. The use of LDL cholesterol targets seriously degraded the accuracy of the 2001 guidelines for statin assignment. The proportion of patients assigned to statin therapy was 15% higher under the new guidelines, which translates to 8.9 million more Americans on statin treatment. The study concludes that the new guidelines match statin assignment to patients' total plaque burden better than the older guidelines, with only a modest increase in the number of patients assigned to statin therapy.

This study is important because it strongly supports prior findings (2) that the 2001 guidelines undertreated especially younger, high-risk patients. The major reason for the undertreatment with the 2001 guidelines resulted from their use of LDL cholesterol goals. The new guidelines appear to reduce this critical limitation. At the same time, by all 3 plaque assessment techniques, the new guidelines recommended statin therapy to fewer subjects without demonstrable disease than did the old guidelines. In short, the present study suggests that the new guidelines are a major clinical and conceptual improvement over the older ones.

Limitations of this study deserve comment, although none totally discount its seminal findings. The select cohort studied was referred for angiography predominately for nonspecific symptoms, indeterminate stress test results, or the presence of multiple risk factors and therefore was at higher than average risk. Although not representative of a true population cross section, only 20% of the men and 13% of the women had known coronary artery disease before angiography. Still, two-thirds of the cohort studied had coronary artery disease. Total and LDL cholesterol baseline values were estimated but not

measured in the majority of subjects who were already on statin treatment. The variability of responses and adherence to therapy limit accurately knowing whether either set of guidelines would recommend treatment. As such, it raises the question of whether we should have a risk estimator that takes into account patients already on statins, as we do for those already on antihypertensive treatment. The study's most important and inescapable limitation is that plaque burden is a good but imperfect predictor of future coronary events. Coronary artery disease is not the same as coronary heart disease, for which we have considerable prospective data on statin efficacy. Plaque density and other local and systemic markers of plaque vulnerability were not measured. The new guidelines advocate the use of coronary calcium scoring and other measures to clarify intermediate risk. Whether coronary calcium and/or angiography should be routinely used in determining the need for statin therapy is a complex, contentious issue that will require prospective evaluation.

Finally, the present study asks the fundamental question of whether guidelines are really distilled wisdom or simply working hypotheses. In a regulatory world in which the quality of medical care, and hence reimbursement, is evaluated by adherence to treatment guidelines, do guidelines need to be prospectively validated? Do we need fewer comments from experts and medical societies and more science? I would argue the latter. So does the present study.

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